New Lithium-Zincate Approaches for the Selective Functionalisation of Pyrazine: Direct Dideprotozincation *vs* Nucleophilic Alkylation

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General: All reactions were performed under a protective argon atmosphere using standard Schlenk techniques. Hexane and THF were dried by heating under reflux over sodium benzophenone ketyl and distilled under nitrogen prior to use. [(THF)Li(TMP)(*t*Bu)Zn(*t*Bu)] was prepared according to literature procedure.[1] 1,4-pyrazine was purchased from Sigma Aldrich chemicals and used as received. PMDETA was distilled over CaH_2 prior to use and stored over molecular sieves. NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer operating at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C. Elemental analyses were attempted using a Perkin Elmer 2400 elemental analyzer; however; due to the extreme air-sensitivity of the compounds satisfactory analyses could not be obtained.

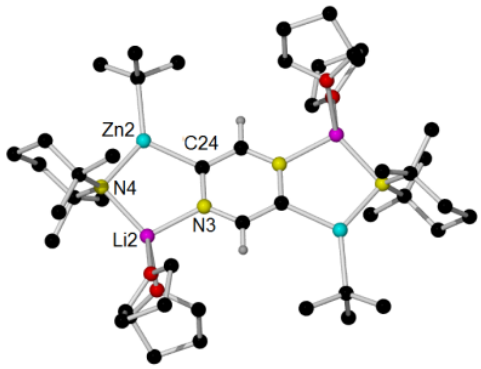
‡**Crystal data for 3**: $C_{46}H_{88}Li_2N_4O_4Zn_2$, M_r = 905.82, monoclinic, space group $P2_1/n$, a = 17.3706(4), b = 16.5165(4), c = 17.8453(6) Å, β =105.038 °, V = 4944.5(2) Å^3, Z = 4, λ = 0.71073 Å, μ = 1.013 mm $^{-1}$, T = 123(2) K; Due to twinning, a SHELX hklf 5 formatted file was produced with 32501 reflection data present; final refinement on F^2 gave R = 0.0846 (F, 21835 obs. data only) and R_w = 0.2390 (F^2, all data), GOF = 1.106, twin ratio refined to 0.674:0.326. **Crystal data for 5:** $C_{25}H_{54}LiN_5Zn$, M_r = 497.04, orthorhombic, space group $P2_12_12_1$, a = 13.0384(8), b = 14.2144(8), c = 16.4829(8) Å, V = 3054.8(3) Å^3, Z = 4, λ = 0.71073 Å, μ = 0.822 mm $^{-1}$, T = 123(2) K; 10176 reflections, 5924 unique, R_{int} = 0.0469; final refinement on F^2 gave R = 0.0447 (F, 3580 obs. data only) and R_w = 0.0580 (F^2, all data), GOF = 0.786, Flack parameter = 0.498(11). **Crystal data for 7:** $C_{40}H_{70}N_8Zn_3$, M_r = 859.15, monoclinic, space group C2/c, a = 27.469(2), b = 12.6321(5), c = 16.5424(11) Å, , β =125.028 °, V = 4700.4(5) Å^3, Z = 4, λ = 0.71073 Å, μ = 1.552 mm $^{-1}$, T = 123(2) K; 15271 reflections, 6041 unique, R_{int} = 0.0402; final refinement on F^2 gave R = 0.0403 (F, 4389 obs. data only) and R_w = 0.0840 (F^2, all data), GOF = 1.024.

Synthesis of [LiZn*t*Bu$_3$.PMDETA] (2) To a solution of tBu$_2$Zn (0.09 g, 0.5 mMol) in hexane (5 mL) *t*BuLi (0.26 mL of a 1.7 M solution, 0.5 mMol) was added to give a colourless solution which was stirred for 1 h. PMDETA (0.11 mL, 0.5 mMol) was added to give a white precipitate. Following 1 h of stirring all volatiles were removed to yield a colourless oil. ^{1}H NMR (400.13 MHz, 298 K d$_8$-THF)

δ ppm: 2.51 (t, 4H, PMDETA-CH_2), 2.41 (t, 4H, PMDETA-CH_2), 2.33 (s, 3H, PMDETA-CH_3), 2.24 (s, 12H, PMDETA-$(CH_3)_4$), 0.91 (s, 27H, *t*Bu). ^{13}C {^1H} (100.62 MHz, 298 K, d_8-THF) δ ppm: 58.21 (PMDETA-CH_2), 55.39 (PMDETA-CH_2), 45.88 (PMDETA-$(CH_3)_4$), 43.90 (PMDETA-CH_3), 36.56 (*t*Bu), 23.93 (q-*t*Bu).

Synthesis of [2,5-{(THF)$_2$LiZn(TMP)^{t}Bu)}$_2$($C_4H_2N_2$)] (3) To a solution of [(THF)Li(TMP)(*t*Bu)Zn(*t*Bu)] (0.8 g, 2 mMol) in 3 mL of THF at 0 °C was added 1,4-pyrazine (0.08 g, 1 mMol) giving an instant bright orange coloured solution. The reaction was allowed to stir at 0 °C for 5 minutes before 1.5 mL of hexane were added and the solution transferred to the refrigerator (-5 °C) to crystallise. After 24 hrs a crop of bright orange/red needle crystals were deposited (0.46 g, 51%). ^1H (400.13 MHz, 298 K, C_6D_6) δ ppm 9.19 (s, 1H, H-pyrazine), 3.48 (m broad, 8H, THF), 1.92 (s broad, 1H, γ-TMP), 1.75 (s broad, 9H, *t*Bu), 1.62 (s broad, 1H, γ-TMP), 1.58 (s broad, 2H, β-TMP), 1.42 (s broad, 6H, Me-TMP), 1.41 (s broad, 8H, THF), 1.29 (s broad, 2H, β-TMP), 1.13 (s broad, 6H, Me-TMP). ^{13}C {^1H} (100.62 MHz, 298 K, C_6D_6) δ ppm: 187.13 (C-Zn), 155.35 (C-H pyrazine), 68.14 (THF), 52.89 (q-TMP), 40.18 (β-TMP), 35.30 (*t*Bu), 35.07 (Me-TMP), 33.52 (Me-TMP), 25.42 (THF), 20.81 (q-*t*Bu), 19.84 (γ-TMP).

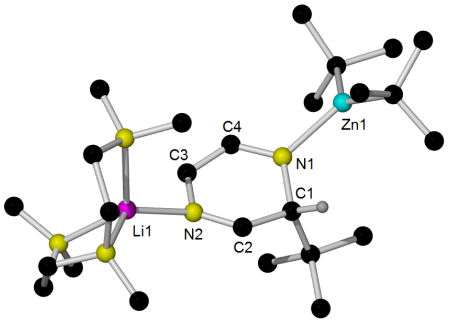
The centrosymmetric molecular structure[11] of **3** (Fig. 1a) confirmed a two-fold deprotonated pyrazine ring substituted at the least congested opposite 2, 5-positions by zinc atoms. Solvated by two THF molecules, Li2 interacts with the N lone pair of the heterocycle giving rise to a near planar arrangement, with both metals lying slightly out of the $C_4H_2N_2$ ring [deviations from the mean plane are -0.253(8) and +0.28(1) Å for Zn and Li respectively]. Bonded to a terminal ^{t}Bu group, trigonal planar Zn2 is connected to Li2 via a TMP bridge, closing a {ZnCNLiN} 5-atom ring which renders a unique three (6,5,6)-ring-fused structure (Figure 1a).



Synthesis of 2,5-diiodopyrazine (4) To a solution of **5** in THF, I_2 (7 mL of a 1 M solution in THF, 7 mMol) was added at 0 °C and allowed to stir for 18 hours at room temperature before addition of saturated aq NH_4Cl (10 mL) and saturated aq $Na_2S_2O_3$ until bleaching (5 mL). The product was extracted with DCM (3 X 10 mL) and the combined organic phases dried ($MgSO_4$), filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (eluent DCM:Hexane 1:1) to give 2,5-diiodopyrazine as an off-white crystalline solid (0.21 g, 68%). ^1H (400.13 MHz, 298 K, $CDCl_3$) δ ppm: 8.63 (s, 2H). ^{13}C {^1H} (100.62 MHz, 298 K, $CDCl_3$) δ ppm: 153.76 (C-H pyrazine) 116.50 (C-I pyrazine) agree with those reported in the literature.

Synthesis of [(PMDETA)Li{$C_4N_2H_4$(^{t}Bu)}Zn^{t}Bu$_2$](5) To a solution of *t*Bu$_2$Zn (0.36 g, 2 mMol) in hexane (10 mL) *t*BuLi (1.17 mL of a 1.7 M solution, 2 mMol) was added to give a colourless solution. PMDETA (0.42 mL, 2 mMol) was added to give a white precipitate. The suspension was allowed to stir at room temperature for 10 minutes before pyrazine (0.16 g, 2 mMol) was added at room temperature, forming a bright yellow oil, and the reaction mixture was placed in the freezer (-27 °C). After 24 hrs a crop of bright yellow crystals were deposited (0.76 g 76%). ^1H (400.13 MHz, 298 K, C_6D_6) δ ppm: 7.16 (s broad, 1H, pyrazine), 5.59 (s broad, 1H, pyrazine), 5.37 (s broad, 1H, pyrazine), 4.08 (s broad, 1H, C-H pyrazine tBu), 1.82 (s broad, 8H, CH_2-PMDETA), 1.78 (s broad, 12H CH_3-PMDETA), 1.71 (s broad, 3H, CH_3-PMDETA), 1.59 (s broad, 18H, 2x *t*Bu-Zn), 1.19 (s, 9H, *t*Bu-pyrazine). ^{13}C {^1H} (100.62 MHz, 298 K, C_6D_6) δ ppm: 145.21 (C-H pyrazine), 123.44 (C-H

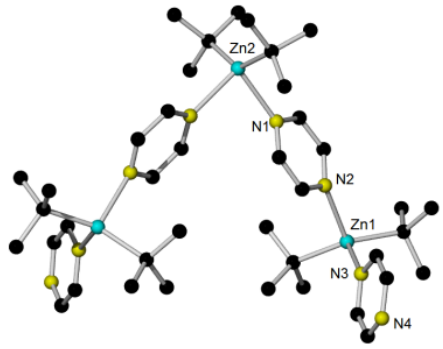
pyrazine), 107.29 (C-H pyrazine), 66.28 (C-tBu-pyrazine), 56.73 (CH_3-PMDETA) 53.21 (CH_3-PMDETA), 44.95 (CH_3-PMDETA), 43.73 (CH_2-PMDETA), 40.72 (q-C-*t*Bu pyrazine ring), 35.55 (Zn-*t*Bu), 25.35 (*t*Bu-pyrazine ring), 22.62 (q-C *t*Bu-Zn).



Established by X-ray crystallography, the structure of **5** (Figure 2a) provided confirmation of the addition of the lithium-zincate **2** across one C=N bond of pyrazine in a 1, 2-fashion, transferring a ^{t}Bu group to C1 (which changes its hybridization from sp^2 to sp^3) to generate a cyclic amide fragment bonded to Zn^{t}Bu$_2$, generating a new Zn-N bond of similar strength (Zn1-N1, 2.021(3) Å) to that found in **2** for the Zn-N_{TMP} bond [2.052(3) Å]. The structure is completed by a PMDETA-solvated Li which coordinates to the lone pair of the remaining pyridine-type N on the ring [Li-N2, 1.981(6) Å] (Figure 2a). Demonstrating its loss of aromaticity, the new heterocyclic ring is noticeably puckered [C1 lies 0.412(6) Å from the least-squares plane defined by the other five atoms of the C4N2 ring] and the C-C and C-N distances involving N1, C1, C2 and N2 show a more localized double/single bond pattern [N1-C1, 1.480(3); C2-C1, 1.504(4); C2-N2, 1.281(4) Å], in comparison with those involving N1, C3, C4 and N2 [N1-C4, 1.338(4) Å; C4-C3, 1.362(5); C3-N2, 1.397(4) Å]. A search in the Cambridge Structural Database revealed no precedents for an alkylated diazine structure of zinc or lithium or indeed of any metal, comparable to **5**. Moreover, as far as we can ascertain, compound **5** represents the first example of a structurally defined reaction intermediate of the nucleophilic addition of a zincate to a C=N of an organic molecule.

Synthesis of 2-(*t*Bu)pyrazine (6) To a solution of *t*Bu_2Zn (0.36 g, 2 mMol) in hexane (10 mL) *t*BuLi (1.17 mL of a 1.7 M solution, 2 mMol) was added to give a colourless solution. PMDETA (0.42 mL, 2 mMol) was added to give a white precipitate. The suspension was allowed to stir at room temperature for 10 minutes before pyrazine (0.16 g, 2 mMol) was added and the reaction mixture stirred at room temperature for 1 hour. The reaction was then quenched with H_2O (5 mL) and the product extracted with DCM (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was then purified by column chromatography on silica gel (eluent : DCM then DCM:EtOAc 4:1) to give the product as an yellow oil (0.22 g, 83%). ^{1}H (400.13 MHz, 298 K, $CDCl_3$) δ ppm: 8.85 (d, 1H, pyrazine), 8.51 (t, 2H, pyrazine), 8.39 (d, 1H, pyrazine), 1.40 (s, 9H, *t*Bu). ^{13}C {^{1}H} (100.62 MHz, 298 K, $CDCl_3$) δ ppm: 143.29 (C-H pyrazine), 141.72 (C-H pyrazine), 141.59 (C-H pyrazine), 29.78 (C-*t*Bu) agree with those reported in the literature.

Synthesis of [{Zn^{t}Bu$_2$}$_3${C$_4$H$_4$N$_2$}$_4$] (7) To a solution of *t*Bu_2Zn (0.36 g, 2 mMol) in hexane (10 mL) pyrazine (0.16 g, 2 mMol) was added to give an orange solution. The solution was placed in the freezer (-27 °C) and a crop of red needle deposited after 24 h (0.18 g, 42% based on pyrazine). ^{1}H NMR (400.13 MHz, 298 K d_8-THF) δ ppm: 8.57 (s broad, 16H, pyrazine), 0.96 (s, 54H, *t*Bu) there is also some residual hexane solvent at 1.27, 0.86. ^{13}C {^{1}H} (100.62 MHz, 298 K, d_8-THF) δ ppm: 145.90 (pyrazine), 32.96 (*t*Bu), 32.41, 23.40 and 14.44 (residual hexane).



Exhibiting an open triangular trinuclear arrangement, the crystal structure of 7 (Fig. 2b) shows that each Zn binds to two unchanged molecules of pyrazine which act as simple 2e- neutral donors through their N atoms, two of them coordinate terminal to the outer Zn atoms (Zn1) whereas the remaining two act as bridges through both N centres connecting central Zn2 with Zn1. As expected the average Zn-N bond distance in 7 (2.284 Å) is significantly elongated to that in 5 (Zn1-N1, 2.021(3) Å) according to the change in the nature of the Zn-N bonding.

DOSY experiments The Diffusion-Ordered Spectroscopy (DOSY) NMR experiment was performed on a Bruker AVANCE 400 NMR spectrometer operating at 400.13 MHz for proton resonance under TopSpin (version 2.0, Bruker Biospin, Karlsruhe) and equipped with a BBFO-z-atm probe with actively shielded z-gradient coil capable of delivering a maximum gradient strength of 54 G/cm. Diffusion ordered NMR data was acquired using the Bruker pulse program dstegp3s employing a double stimulated echo with three spoiling gradients. Sine-shaped gradient pulses were used with a duration of 3 ms together with a diffusion period of 100 ms. Gradient recovery delays of 200 µs followed the application of each gradient pulse. Data was accumulated by linearly varying the diffusion encoding gradients over a range from 2% to 95% of maximum for 64 gradient increment values. DOSY plot was generated by use of the DOSY processing module of TopSpin. Parameters were optimized empirically to find the best quality of data for presentation purposes. Diffusion coefficients were calculated by fitting intensity data to the Stejskal-Tanner expression with estimates of errors taken from the variability in the calculated diffusion coefficients by consideration of different NMR responses for the same molecules of interest (except TMS).

To obtain some information about the complexation of LiCl to Zn*t*Bu$_2$ in solution their diffusion properties were studied by DOSY NMR experiments. DOSY techniques can be used to identify individual components of solution mixtures (comparable to chromatography in NMR terms) and to estimate their sizes, which are inversely proportional to their diffusion coefficients (D). To obtain accurate hydrodynamic and avoid misleading results that single diffusion measurements can produce, DOSY measurements can be run in the presence of internal standards of known molecular weight.

Diffusion study of [Zn*t*Bu$_2$]: ^{1}H DOSY NMR experiment of [Zn*t*Bu$_2$] with internal references present (tetraphenylnaphthalene TPhN, phenylnaphthalene PhN and tetramethylsilane, TMS) was recorded at 15 °C in d$_8$-THF (Figure S1). All the different components of the mixture separate clearly in the diffusion dimension with a relative size sequence of TPhN >> PhN = Zn*t*Bu$_2$ >> TMS (Figure S2), according to their increasing D values [D(TPhN) = 6.91 x 10^{-10} m^2 s^{-1} << D(PhN) = 1.17 x 10^{-9} m^2 s^{-1} = D(Zn*t*Bu$_2$) = 1.12 x 10^{-9} m^2 s^{-1} <<D(TMS) = 1.83 x 10^{-9} m^2 s^{-1} (Table S1).

Figure S1 ^{1}H NMR spectrum of Zn*t*Bu$_2$ with standards TPhN, PhN and TMS at 15 °C in d$_8$-THF.

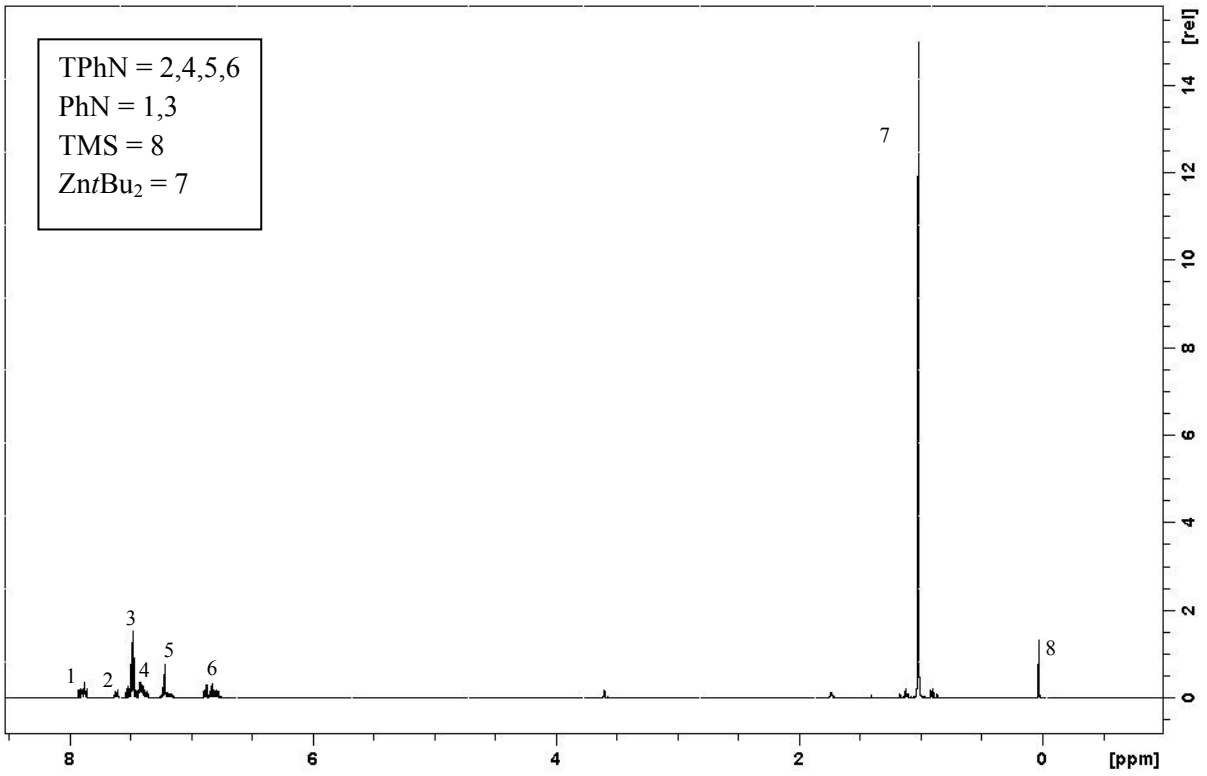


Figure S2 ^{1}H DOSY NMR spectrum of Zn*t*Bu$_2$ with standards TPhN, PhN and TMS at 15 °C in d$_8$-THF.

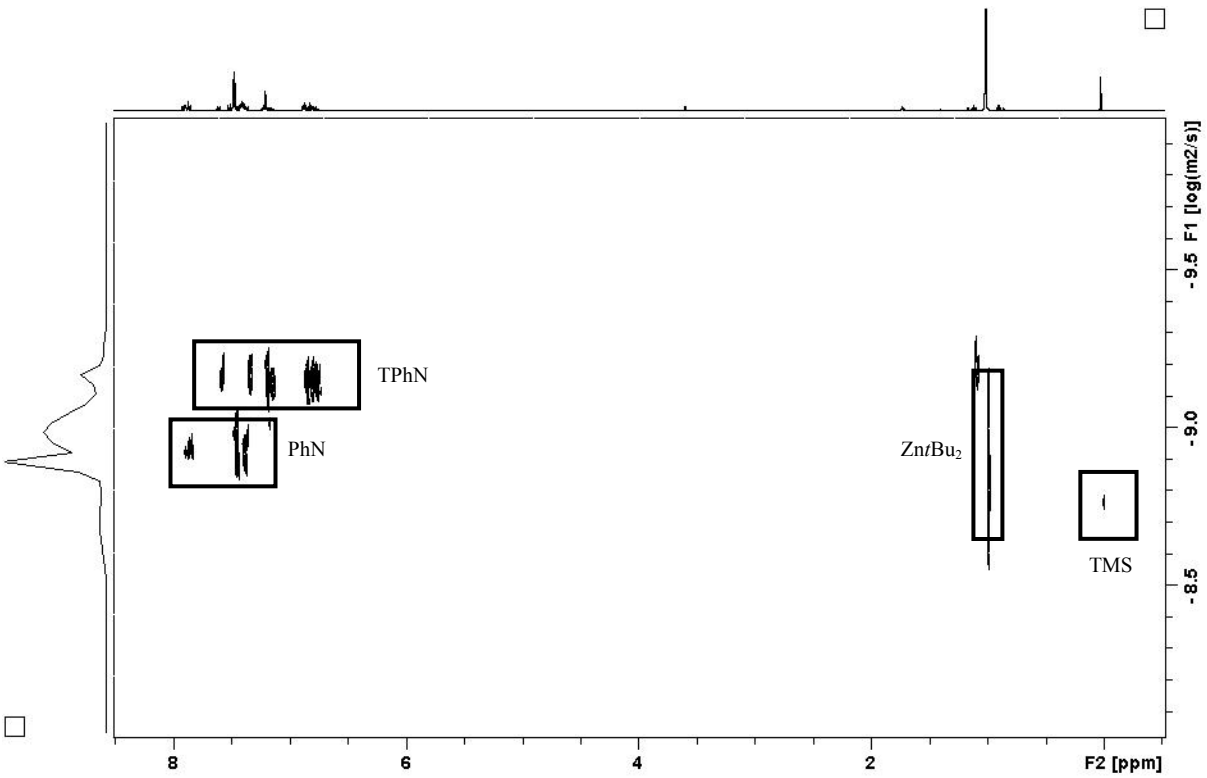


Table S1 Analysis from the ^{1}H DOSY NMR data obtained for the mixture of Zn*t*Bu$_2$ with standards TPhN, PhN and TMS at 15 °C in d$_8$-THF.

Compound	10^{-10} D(m^2/s)
TPhN	6.91
PhN	11.71
TMS	18.32
Zn*t*Bu$_2$	11.19

Diffusion studies of [Zn*t*Bu$_2$.nLiCl] (n = 1-2): ^{1}H DOSY NMR experiments of [Zn*t*Bu$_2$.nLiCl] (where n = 1-4) with internal references present (tetraphenylnaphthalene TPhN, phenylnaphthalene PhN and tetramethylsilane, TMS) were recorded at 15 °C in d$_8$-THF increasing the equivalents of LiCl from 1 equivalent to 4 equivalents to ascertain the extent of complexation of LiCl to Zn*t*Bu$_2$.

Diffusion study of [Zn*t*Bu$_2$.LiCl] All the different components of the mixture separate clearly in the diffusion dimension with a relative size sequence of TPhN > [Zn*t*Bu$_2$.LiCl] > PhN >> TMS (Figures S3 and S4), according to their increasing D values [D(TPhN) = 6.80 x 10^{-10} m^2 s^{-1} < D(Zn*t*Bu$_2$.LiCl) = 8.77 x 10^{-9} m^2 s^{-1} D(PhN) = 1.16 x 10^{-9} m^2 s^{-1} <<D(TMS) = 1.84 x 10^{-9} m^2 s^{-1}(Table S2).

Figure S3 ^{1}H NMR spectrum of Zn*t*Bu$_2$.LiCl with standards TPhN, PhN and TMS at 15 °C in d$_8$-THF.

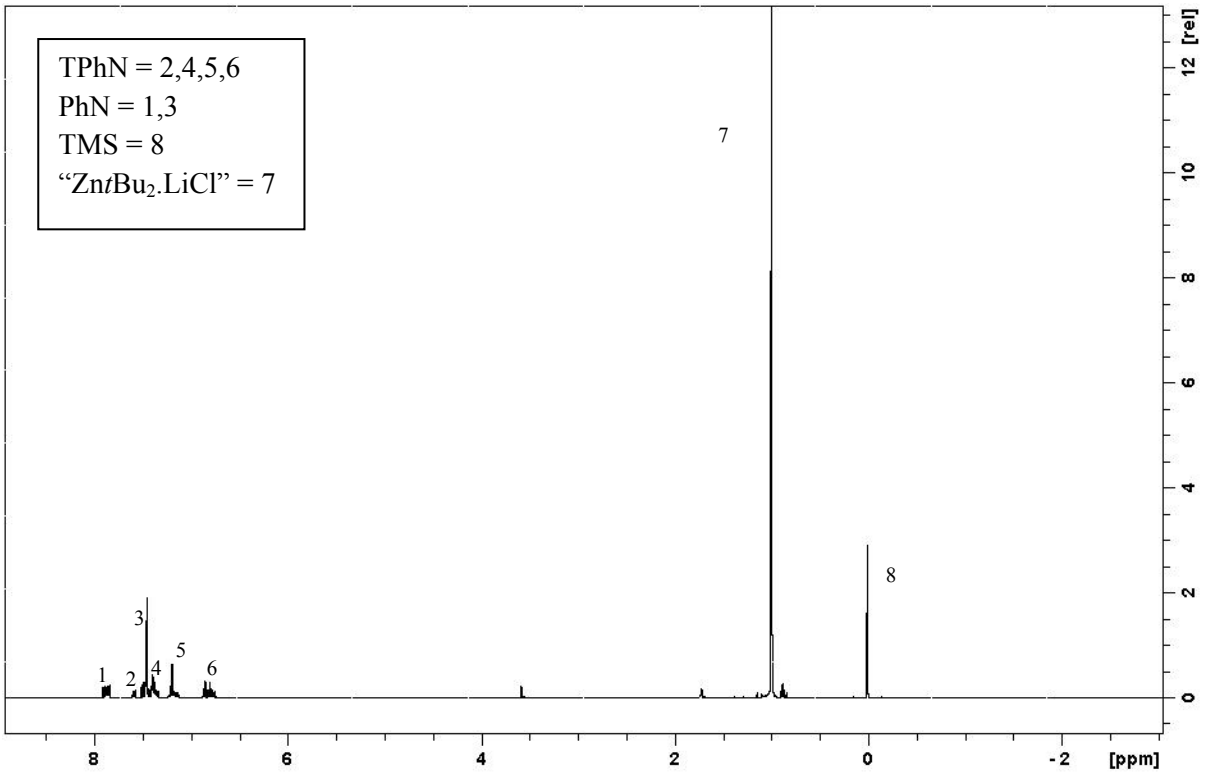


Figure S4 ^{1}H DOSY NMR spectrum of Zn*t*Bu$_2$.LiCl with standards TPhN, PhN and TMS at 15 °C in d_8-THF.

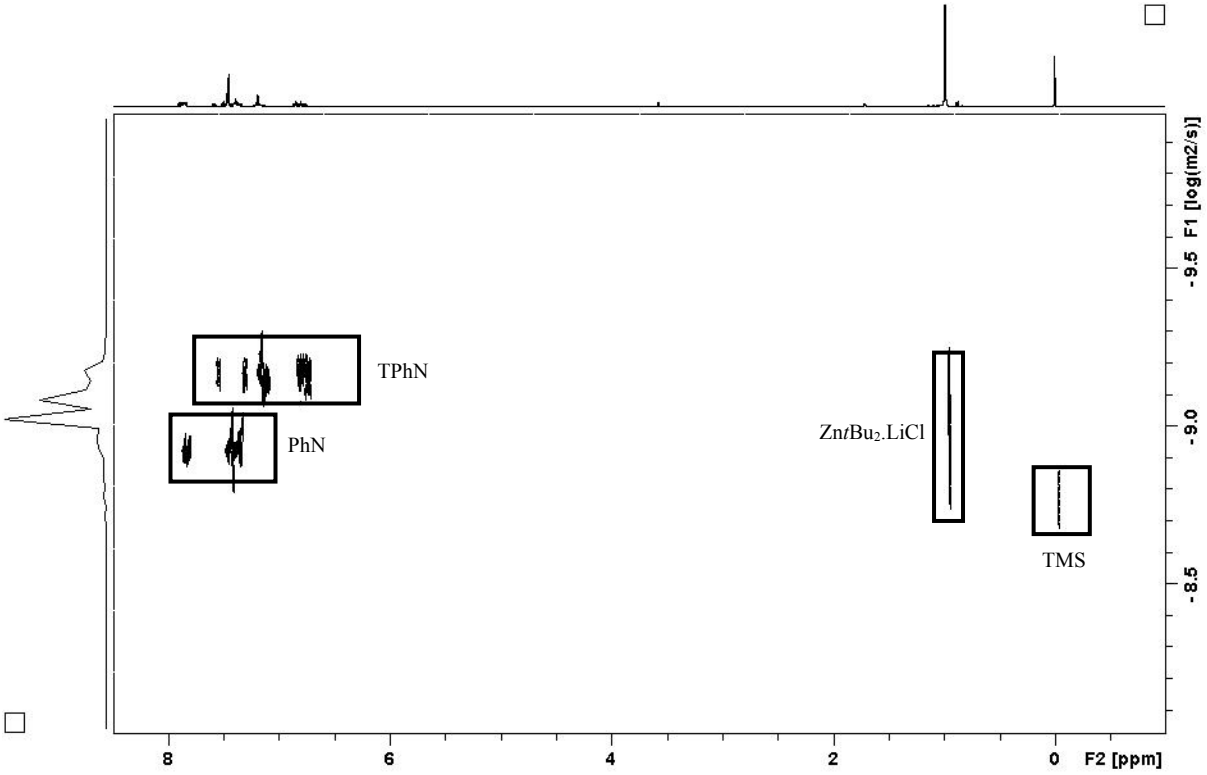


Table S2 Analysis from the ^{1}H DOSY NMR data obtained for the mixture of Zn*t*Bu$_2$.LiCl with standards TPhN, PhN and TMS at 15 °C in d_8-THF.

Compound	10^{-10} D(m^2/s)
TPhN	6.80
PhN	11.55
TMS	18.44
Zn*t*Bu$_2$.LiCl	8.77

Diffusion study of [Zn*t*Bu$_2$.2LiCl] All the different components of the mixture separate clearly in the diffusion dimension with a relative size sequence of TPhN > [Zn*t*Bu$_2$.2LiCl] > PhN >> TMS (Figures S5 and S6), according to their increasing D values [D(TPhN) = 6.27 x 10^{-10} m^2 s^{-1} < D(Zn*t*Bu$_2$.2LiCl) = 7.20 x 10^{-9} m^2 s^{-1} D(PhN) = 1.08 x 10^{-9} m^2 s^{-1} <<D(TMS) = 1.64 x 10^{-9} m^2 s^{-1}(Table S3).

Figure S5 ^{1}H NMR spectrum of Zn*t*Bu$_2$.2LiCl with standards TPhN, PhN and TMS at 15 °C in d$_8$-THF.

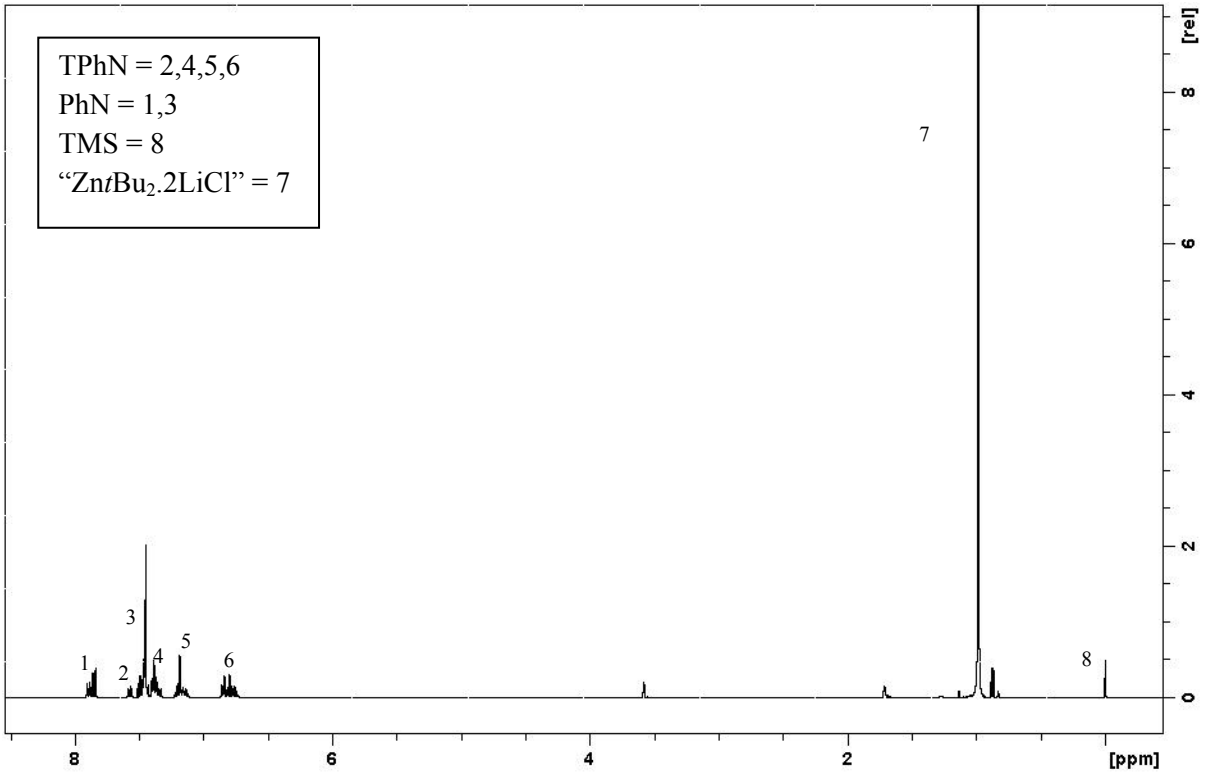


Figure S6 ^{1}H DOSY NMR spectrum of Zn*t*Bu$_2$2LiCl with standards TPhN, PhN and TMS at 15 °C in d$_8$-THF.

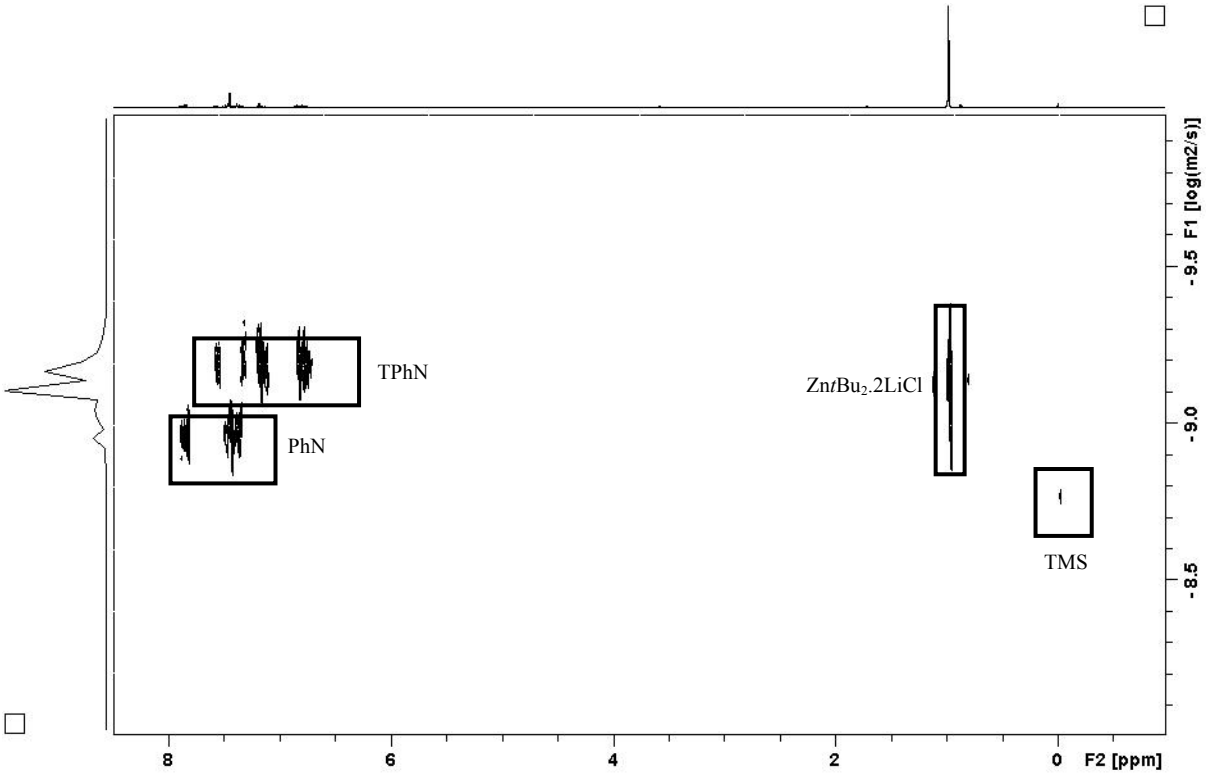


Table S3 Analysis from the ^{1}H DOSY NMR data obtained for the mixture of Zn*t*Bu$_2$.2LiCl with standards TPhN, PhN and TMS at 15 °C in d$_8$-THF.

Compound	10^{-10} D(m^2/s)
TPhN	6.27
PhN	10.83
TMS	16.41
Zn*t*Bu$_2$.2LiCl	7.20

Figure S7 shows the diffusion constants of Zn*t*Bu$_2$.nLiCl (n = 0-2) (purple) compared with the standards (TMS, blue; PhN, red; TPhN, green), with the diffusion constant decreasing as the size of the zinc species increases.

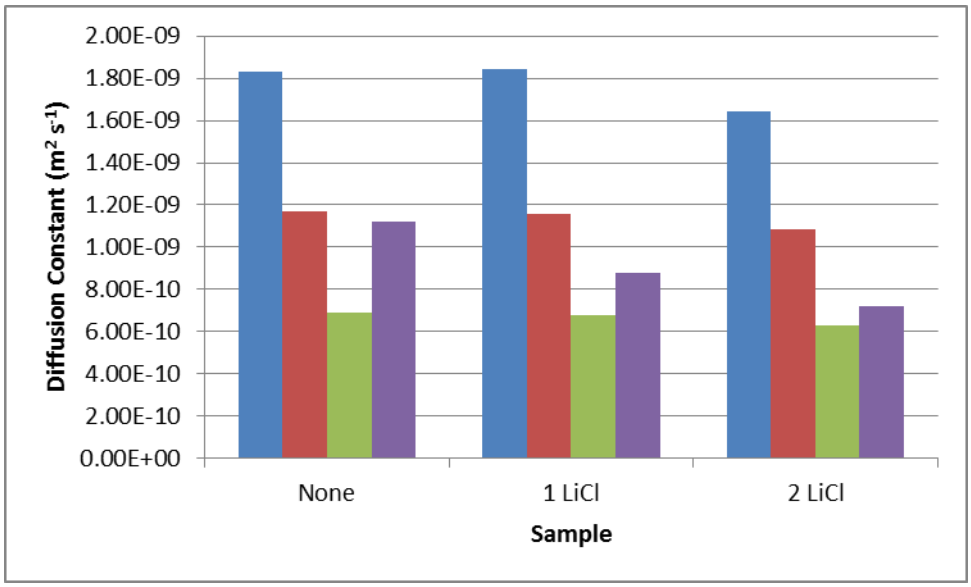
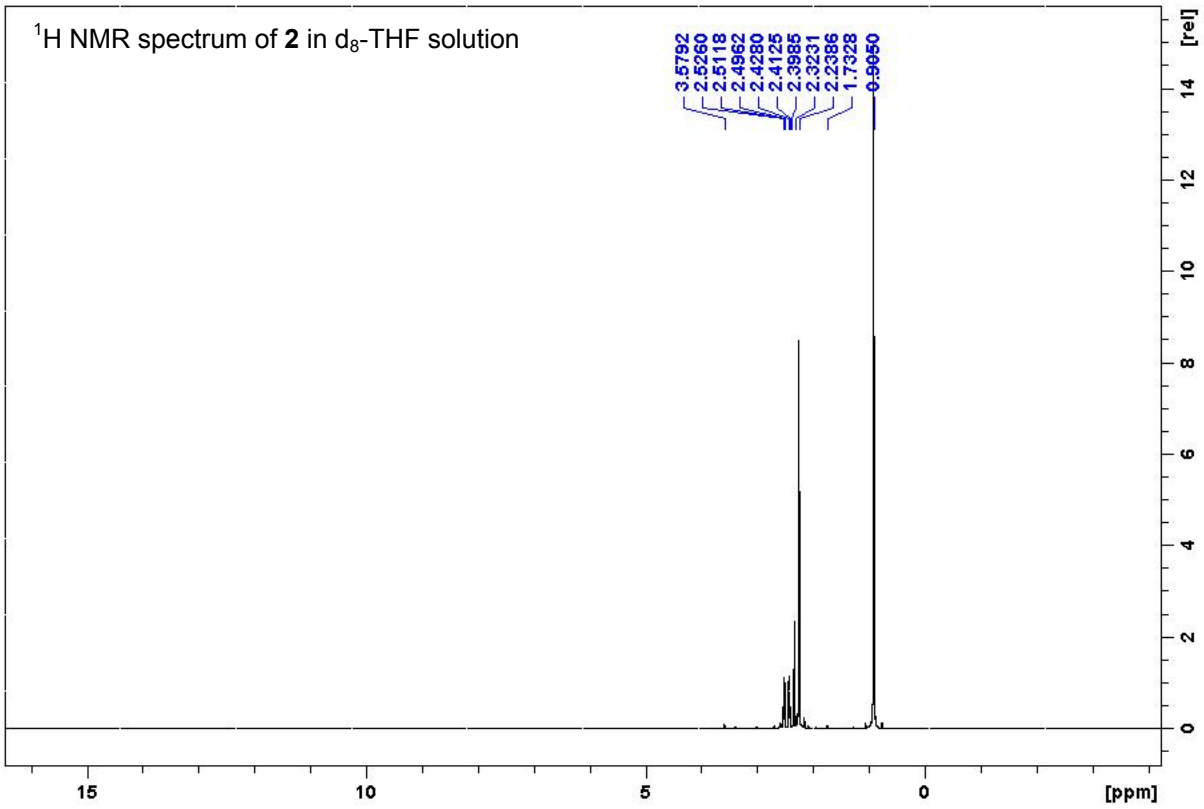
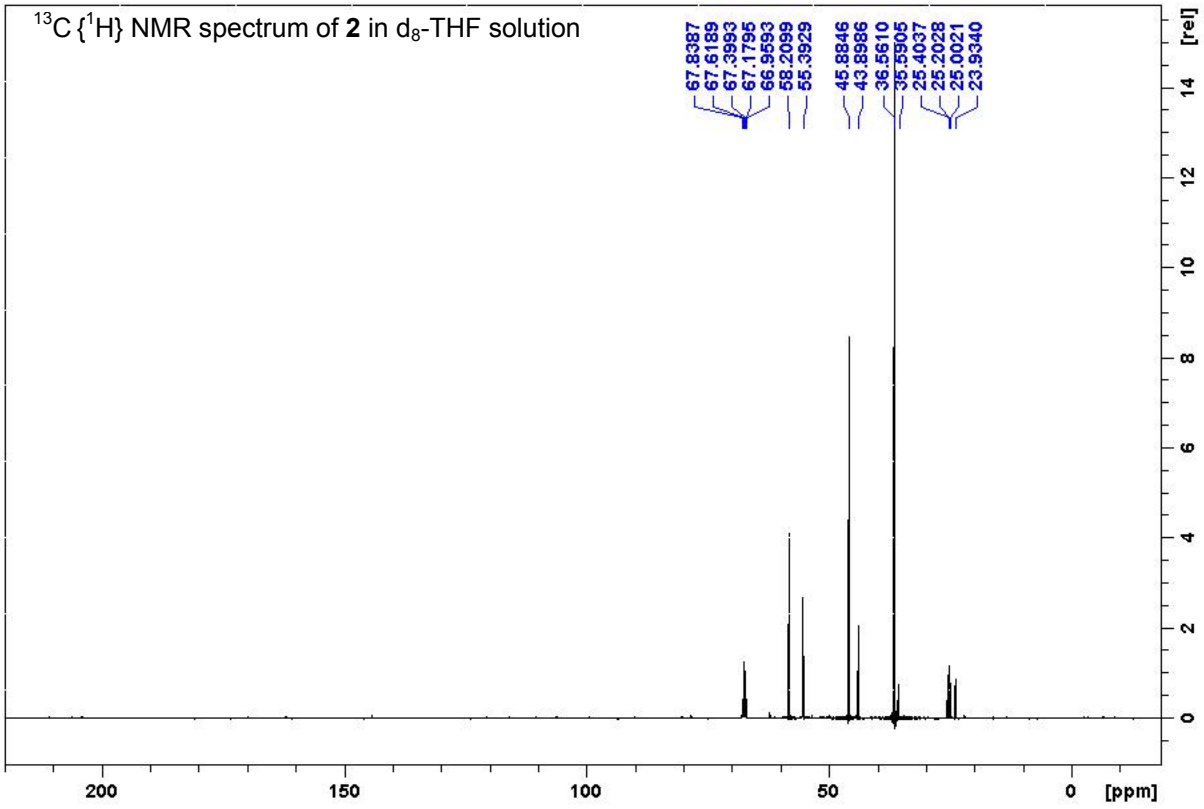


Figure S7 Diffusion constants for TMS (blue), PhN (red), TPhN (green) and sample in purple.

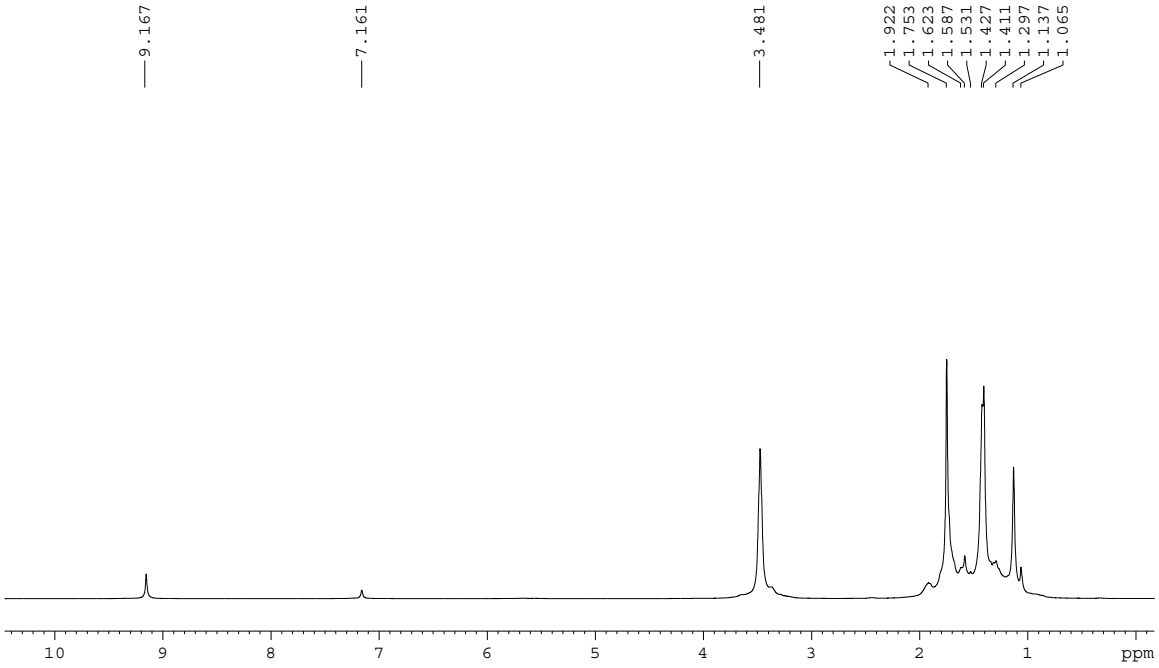
^{1}H NMR spectrum of **2** in d_8-THF solution



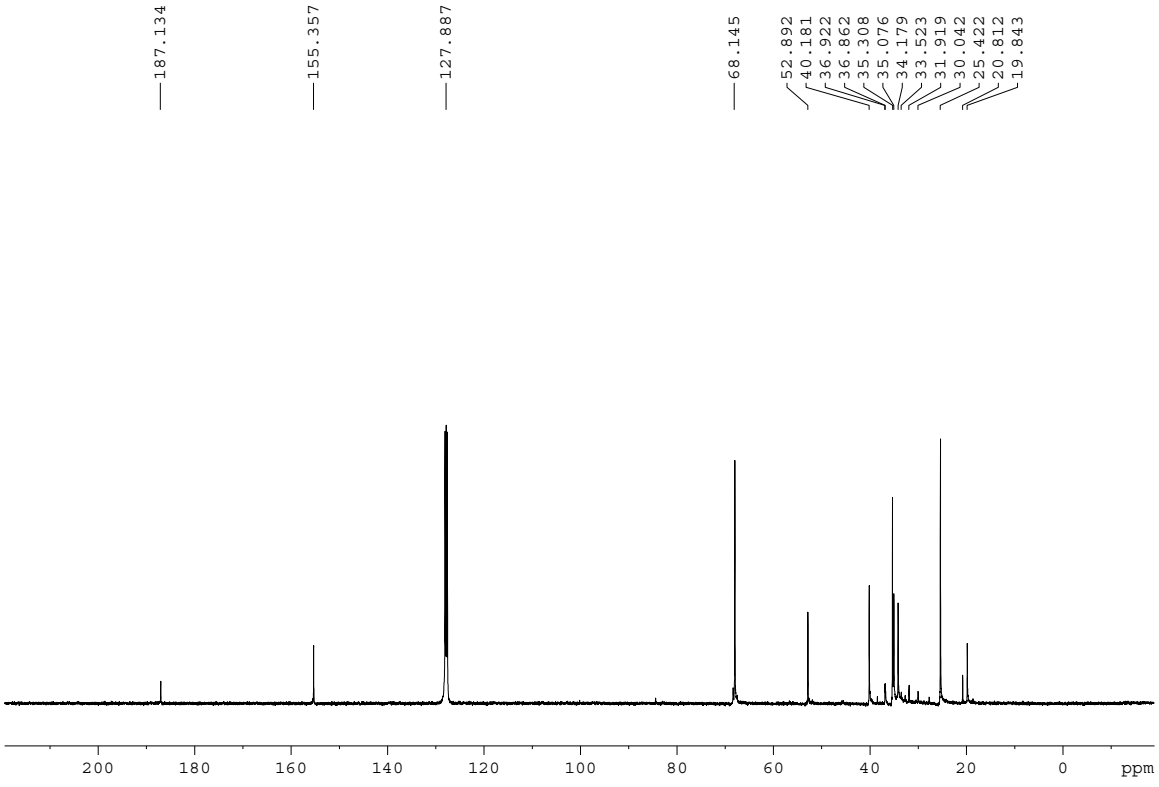
^{13}C {^{1}H} NMR spectrum of **2** in d_8-THF solution



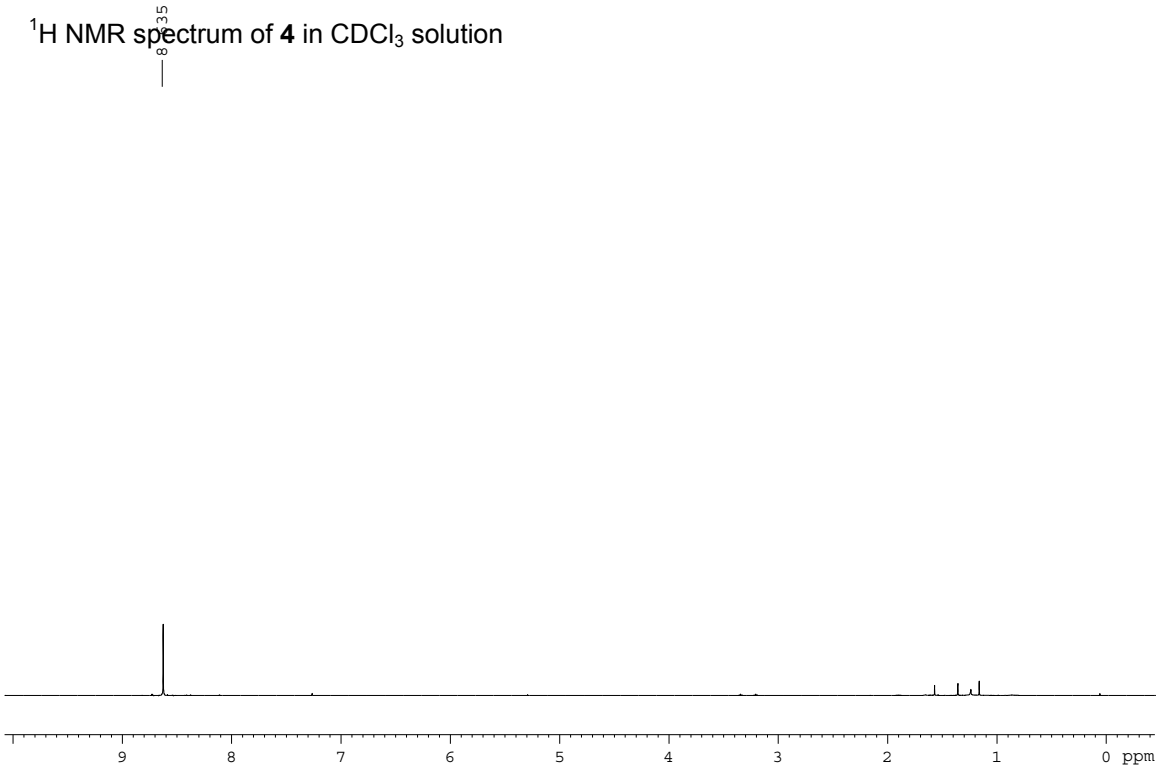
^{1}H NMR spectrum of **3** in C_6D_6 solution



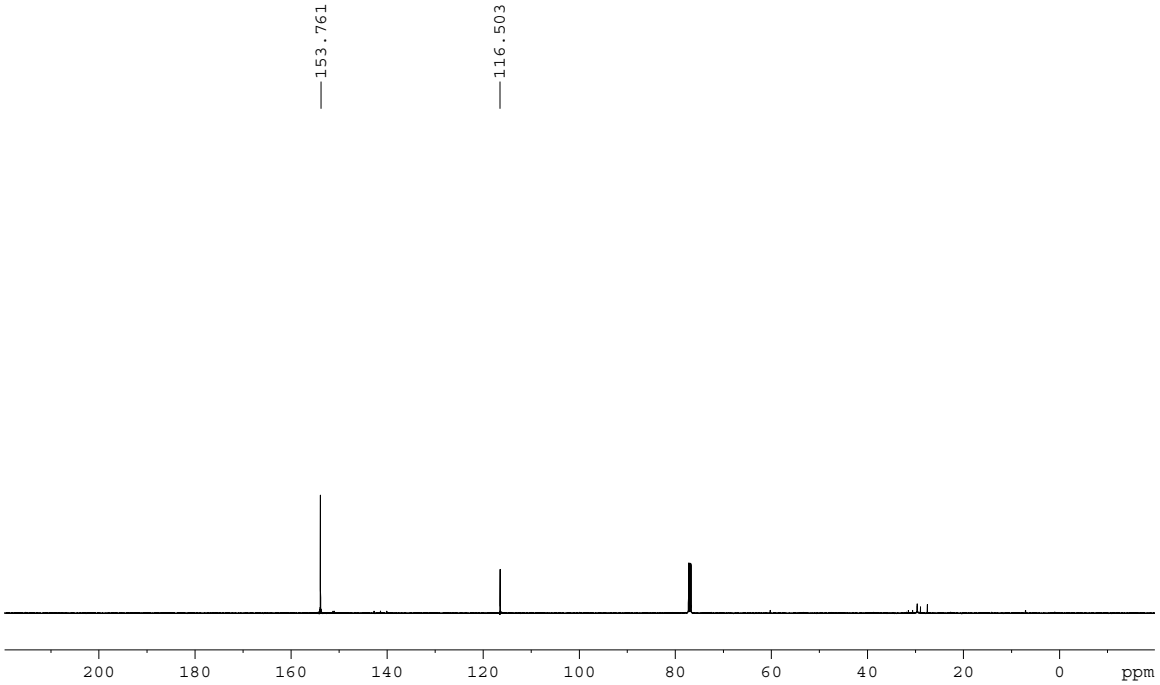
$^{13}C\{^{1}H\}$ NMR spectrum of **3** in C_6D_6 solution



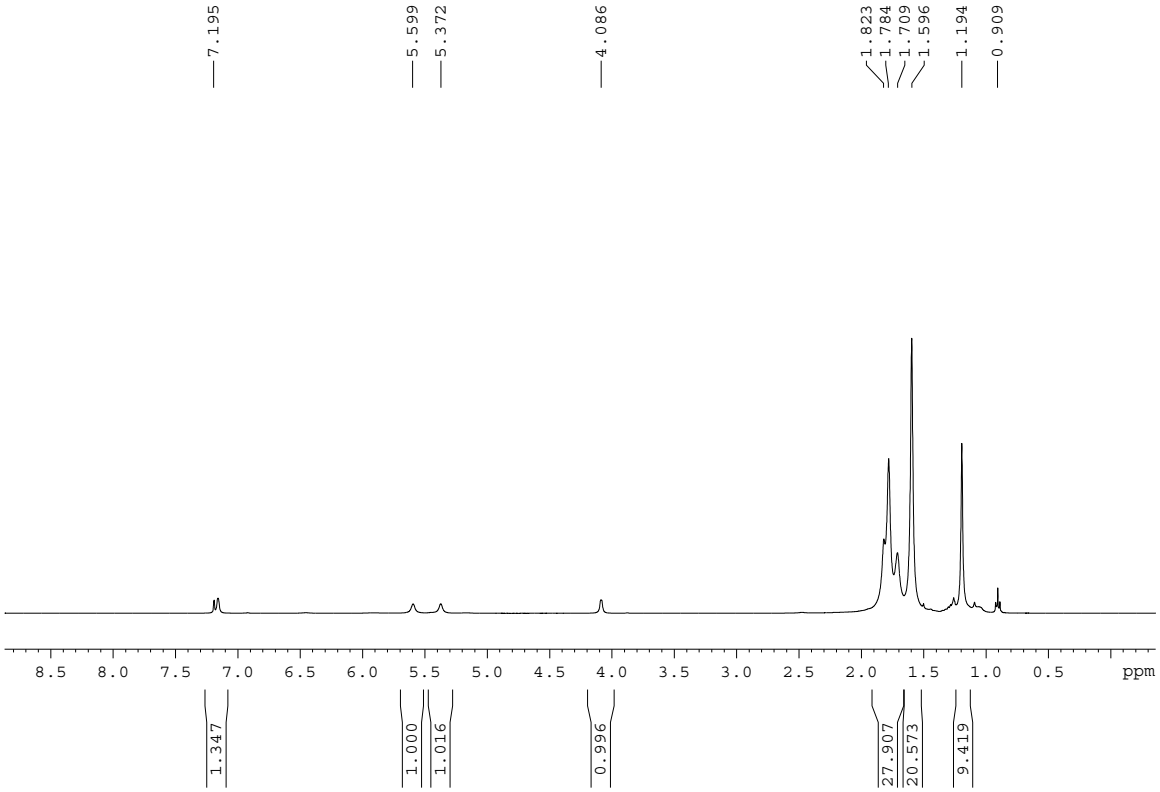
^{1}H NMR spectrum of **4** in $CDCl_3$ solution



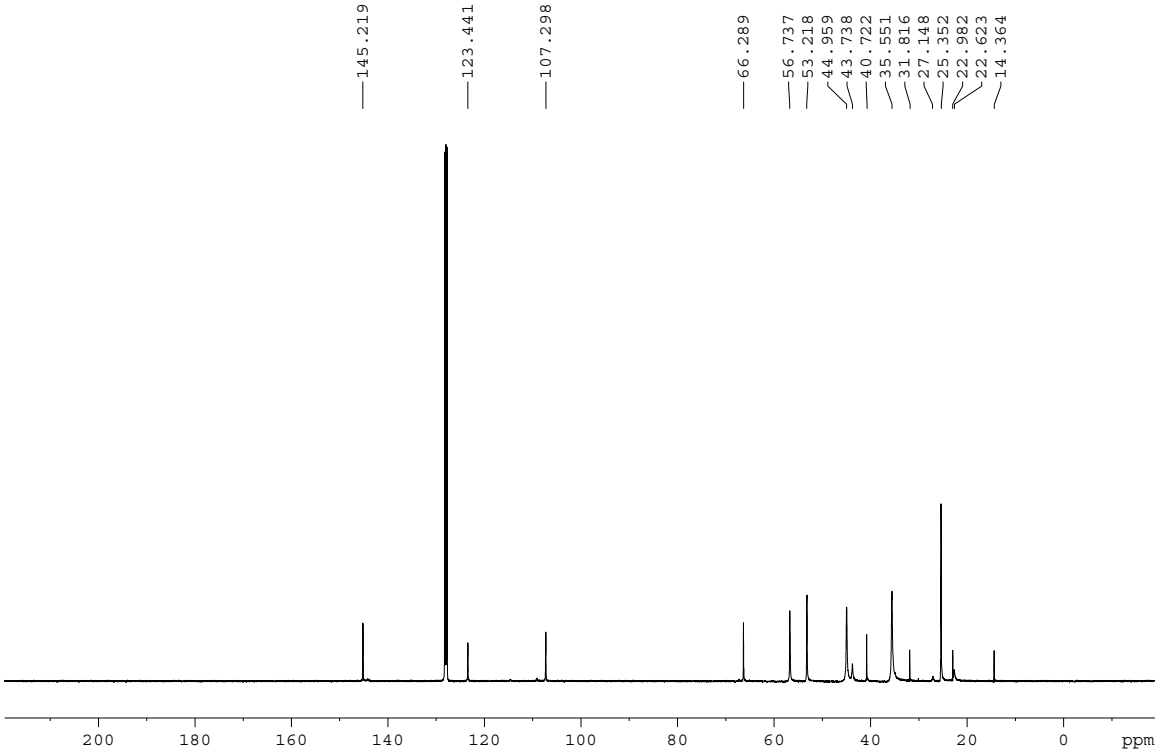
^{13}C {^{1}H} NMR spectrum of **4** in $CDCl_3$ solution



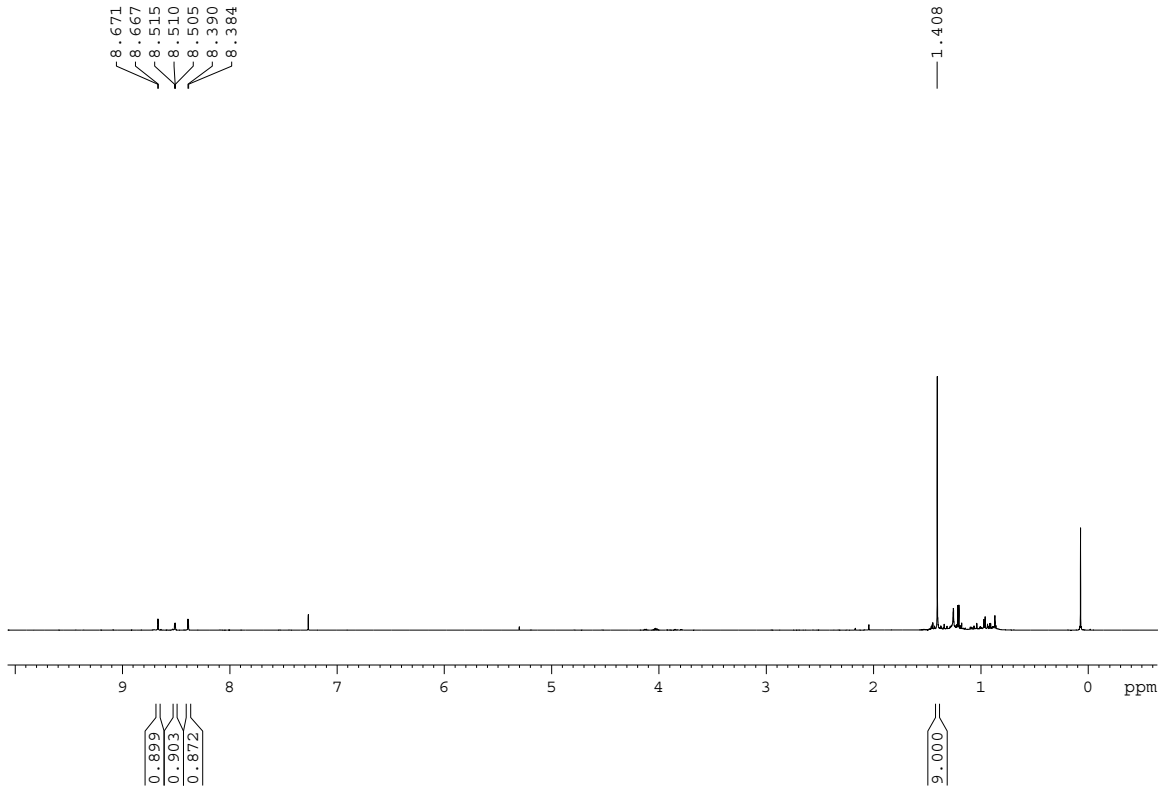
^{1}H NMR spectrum of **5** in C_6D_6 solution



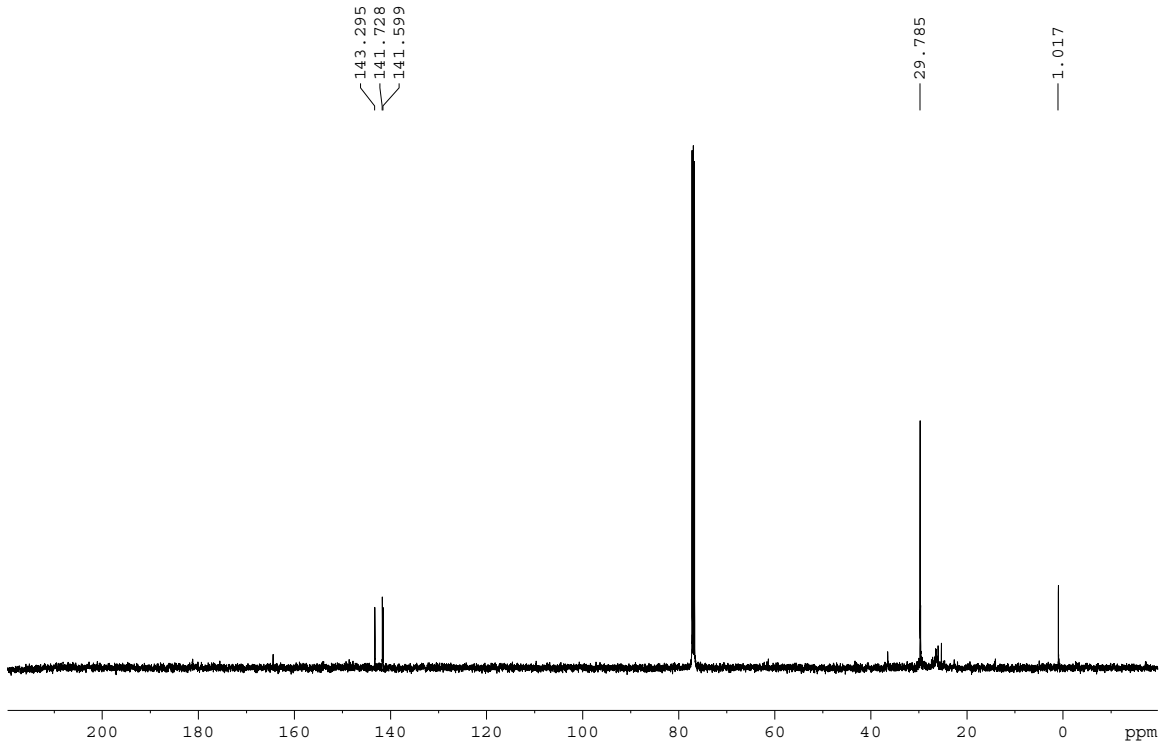
^{13}C {^{1}H} NMR spectrum of **5** in C_6D_6 solution



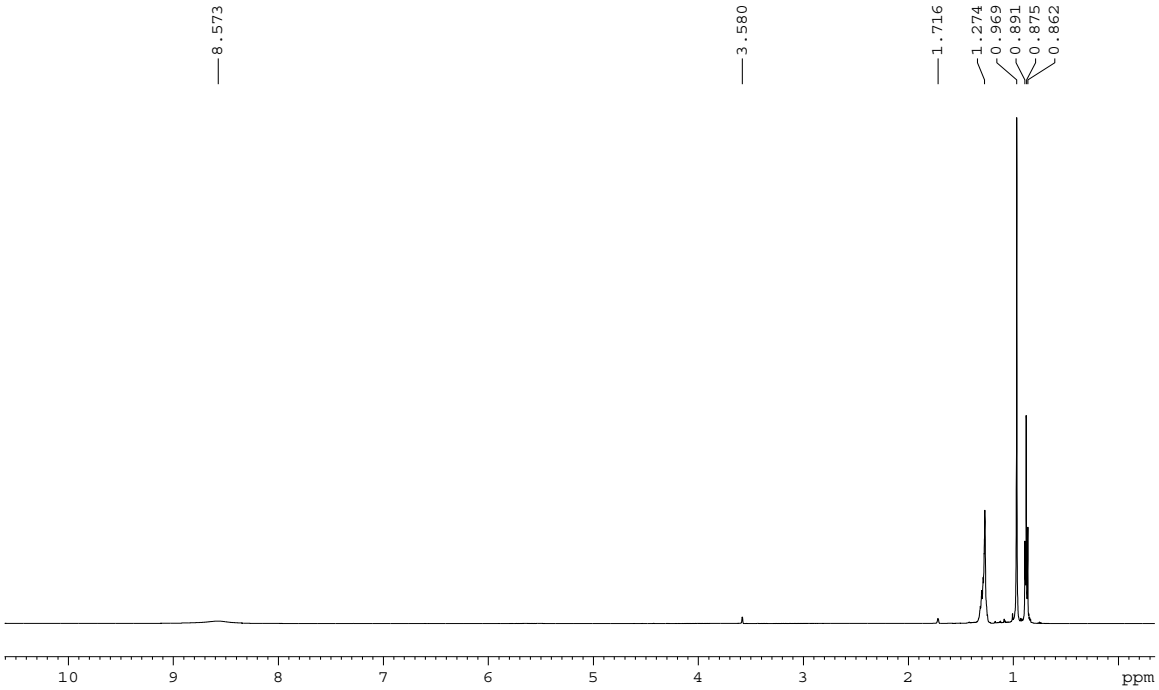
^{1}H NMR spectrum of **6** in C_6D_6 solution



^{13}C {^{1}H} NMR spectrum of **6** in C_6D_6 solution



^{1}H NMR spectrum of **7** in C_6D_6 solution



^{13}C {^{1}H} NMR spectrum of **7** in C_6D_6 solution